

## REMARKS/ARGUMENTS

### STATUS OF THE CLAIMS

Claims 1, 3-10, 13-19, 21-56, 61, 201-221, and 304-308 are pending with entry of this amendment, claims 304-308 being added herein and claims 59-60 being cancelled herein, claims 14-17 and 201-221 having been withdrawn and claims 2, 11-12, 20, 57-58, 62-200, and 222-303 having been cancelled previously. Claims 5, 21-25, 29-33, 35-38, 40-42, and 44-46 are amended herein. These amendments introduce no new matter and support is replete throughout the specification. These amendments are made without prejudice to renewal of the claims in their original form and are not to be construed as abandonment or dedication of the previously claimed subject matter or agreement with any objection or rejection of record.

With respect to the amendments to the claims, support for the amendments can be found throughout the specification. Claim 5 has been amended and claim 308 has been added to more clearly claim the desired invention by presenting alternatives in separate claims; support for the amendments to claim 5, and support for new claim 308, can be found, e.g., in the specification at paragraph [0207] as well as in claim 5 as originally filed. With respect to claims 21-25, 29-33, 35-38, 40-42, and 44-46 and new claims 304-307, support for the amendments can be found throughout the specification. In addition, support for new claim 304 is found in claims 2 and 21 as originally filed; support for new claim 305 is found in claims 2 and 29 as originally filed; support for new claim 306 is found in claims 2 and 36 as originally filed; and support for new claim 307 is found in claims 2 and 45 as originally filed. The dependency of claims 22-25 is amended for consistency with the amendments to claim 21; the dependency of claims 30-33 and 35 is amended for consistency with the amendments to claim 29; the dependency of claims 37-38, 40-42, and 44 is amended for consistency with the amendments to claim 36; and the dependency of claim 46 is amended for consistency with the amendments to claim 45.

Applicants submit that no new matter has been added to the application by way of the above claim amendments. Accordingly, entry of the Amendment is respectfully requested.

Applicants note with appreciation the Examiner's indication of allowable subject matter and withdrawal of previous rejections.

As an initial matter, Applicants would like to thank the Examiner and the Supervisory Patent Examiner for the courtesy extended to the undersigned (Monicia Elrod-Erickson) in conducting a telephone interview with the Examiner and the Supervisory Patent Examiner on May 3, 2007, in which the claim rejections under 35 USC §112 for indefiniteness and the art by Ting et al., Burbaum et al., and Walker et al., particularly with respect to the rejections under 35 USC §103 and lack of motivation to combine these references, was discussed.

The action of January 18, 2007 included: rejections for alleged indefiniteness (items 3-5), rejections for alleged obviousness (items 6-8), and indication of allowable subject matter (item 9). Applicants traverse all rejections and objections, to the extent that they may be applied to the amended claims, for the reasons noted herein.

THE CLAIMS, AS AMENDED, ARE DEFINITE (ACTION ITEMS 3-5)

Item 3

Claims 21-46 were rejected under 35 USC §112, second paragraph, for alleged indefiniteness because it was allegedly unclear in claims 21, 29, 36, and 45 whether the composition is intended to include a cell comprising a first enzyme and caged sensor and a separate enzyme and caged sensor outside of the cell, the same enzyme and caged sensor, or more than one enzyme and caged sensor inside the cell. To the extent that the rejections are applied to the amended claims, Applicants traverse.

Applicants note that claims 21, 29, 36, and 45 as originally filed were multiply dependent on claims 1 and 2. In a previous Action (mailed December 16, 2005), the Examiner indicated these claims were objected to as being dependent upon a rejected base claim but would be allowable if rewritten in independent form including all the limitations of the base claim and any intervening claims. Applicants amended the claims accordingly. The claims at issue clearly specify that the composition includes "a cell comprising an enzyme and a caged sensor" or "an enzyme and a caged sensor."

In the interest of expediting prosecution, however, Applicants have separated these options into separate claims, as discussed with the Examiner, by amending claims 21, 29, 36, and 45 to specify that the composition includes a cell comprising an enzyme and a caged sensor and introducing new claims 304-307 which specify that the composition includes an enzyme and a caged sensor. The dependency of dependent claims 22-25, 30-33, 35, 37-38, 40-42, 44, and 46 is amended accordingly.

Accordingly, Applicants respectfully request that the rejections be withdrawn.

Item 4

Claims 27, 34, and 43 were rejected under 35 USC §112, second paragraph, for alleged indefiniteness, for alleged lack of antecedent basis for "the second caging groups" and because it was allegedly unclear how the second caging groups are related to the composition and whether they are present on the substrate. Applicants respectfully traverse.

In the interview of May 3, 2007, the Examiner's attention was directed to claims 26, 33, and 42, from which claims 27, 34, and 43 (respectively) depend. Antecedent basis for the second caging groups is provided in claims 26, 33, and 42; therefore, there is sufficient antecedent basis for this limitation in claims 27, 34, and 43. Furthermore, as indicated in claims 26, 33, and 42, the second caging groups are associated with the phosphobinder.

As discussed with the Examiner, antecedent basis for the second caging groups is provided, and their relation to the composition is clearly defined. Accordingly, Applicants respectfully request that the rejections be withdrawn.

Item 5

Claims 59 and 60 were rejected under 35 USC §112, second paragraph, for alleged indefiniteness because it was allegedly unclear whether the matrix is part of the composition and whether the caged sensor comprises the matrix.

Applicants note that claim 59 specifies that the sensor includes the first oligonucleotide, which is complementary to and thus capable of binding to the second, matrix-bound oligonucleotide; there is no requirement that the second oligonucleotide or the matrix be part of the composition. However, in the interest of expediting prosecution, Applicants have cancelled claims 59-60, rendering the rejection moot.

THE CLAIMS ARE NOT OBVIOUS (ACTION ITEMS 6-8)

Item 6

Claims 1, 6, 9-10, 18, 21, 23-25, and 29-32 were rejected for alleged obviousness under 35 USC 103(a) over Ting et al. in view of Burbaum et al. further in view of Walker et al. Applicants respectfully traverse these rejections.

Three requirements must be met for a *prima facie* case of obviousness. First, the prior art reference(s) must teach all of the limitations of the claims (M.P.E.P. § 2143.03). Second, there must be a motivation to modify the reference or combine the teachings to produce the claimed invention (M.P.E.P. § 2143.01). Third, a reasonable expectation of success is required (M.P.E.P. § 2143.02). The teaching or suggestion to combine and the expectation of success must be both found in the prior art and not based on Applicants' disclosure (M.P.E.P. § 2143).

The combination of Ting, Burbaum, and Walker does not meet the requirements for a *prima facie* case of obviousness.

As discussed with the Examiner, motivation to combine the teachings of Ting, Burbaum, and Walker by including in the composition of Ting the substrate being caged as taught by Burbaum, as suggested in the Action, is lacking. The Action states that Ting teaches a composition comprising a cell, a kinase, and the sensor. Applicants note that the fluorescent protein constructs described by Ting are expressed in a cell. See, e.g., the first paragraph on page 15003: "Here, we describe a class of FRET-based indicators that are genetically encoded (allowing for simple transfection rather than microinjection..."; see also the section entitled "Gene Construction" on pages 15003-15004. There is thus no motivation to combine the protein constructs of Ting, which are expressed *in vivo* from recombinant nucleic acid constructs, with the caged substrates of Burbaum or the caged peptides of Walker, which are chemically synthesized *in vitro*.

In addition, also as discussed with the Examiner, a *prima facie* case of obviousness cannot be established where the proposed combination of references changes the principal of operation of the prior art invention being modified (M.P.E.P. § 2143.01). As noted above, the protein constructs described by Ting are produced by expression in a cell. Combining one of these constructs with the teachings of Burbaum and Walker would require the protein

construct to be chemically synthesized, and this would require modification of the principal of operation of this construct as described.

No specific suggestion or motivation is found in Ting, Burbaum, or Walker to combine the teachings of the two references to produce a caged sensor like those of the present invention. The Examiner's argument that the references be combined therefore involves an improper hindsight reconstruction of the invention.

Moreover, a reasonable expectation of success has not been demonstrated. For example, as noted above, the protein constructs described in Ting are produced by expression in a cell, while the caged substrates of Burbaum and the caged peptides of Walker are produced by *in vitro* chemical synthesis. In addition, for claims as detailed below, there is no reasonable expectation of success since the suggested combination does not result in the present invention.

The combination of Ting, Burbaum, and Walker fails to teach all the limitations of the claims, particularly claims 21 (and corresponding new claim 304), 23-25, and 30. With respect to claim 21 (and, similarly, claim 304), although the Action notes that "Ting et al. further teach the polypeptide comprising a second label wherein the first and second labels interact to produce the first signal when a substrate is not phosphorylated and a second signal when the substrate is phosphorylated," Applicants note that the constructs of Ting actually operate in the reverse fashion. As illustrated in Figure 1a of Ting, the YFP and GFP moieties do not interact when the substrate is not phosphorylated, and do interact when the substrate is phosphorylated. The combination of Ting, Burbaum, and Walker thus fails to teach all the limitations of claim 21, which specifies that the labels interact when the substrate is not phosphorylated and do not interact when the substrate is phosphorylated. Additional points of distinction are present in the dependent claims, but because independent claim 21 (and, similarly, new claim 304) is not anticipated, it is not necessary to address each additional point. With respect to claim 30, the combination fails to teach at least location of the one or more caging groups on a residue phosphorylated by the kinase.

Applicants note that, although the Action alleges that Burbaum teaches a caged enzyme substrate placed into a cell at column 7 lines 36-47, the noted section of Burbaum does not mention introduction of the substrate into a cell. On the contrary, the substrate of

Burbaum is repeatedly described as being provided in the media and used for detection of a secreted reporter enzyme; see, e.g., column 8 lines 12-15, column 21 lines 39-45, and column 23 lines 5-19.

Because motivation for combining the teachings of Ting, Burbaum, and Walker is lacking, because there is no reasonable expectation of success, and because the combination does not include all the limitations of the claims as indicated, the rejections should be withdrawn.

Item 7

Claims 13, 19, 22, 30, and 61 were rejected for alleged obviousness under 35 USC 103(a) over Ting et al. in view of Burbaum et al. further in view of Walker et al. and Kris et al. Applicants respectfully traverse these rejections.

The combination of Ting, Burbaum, Walker, and Kris does not meet the requirements for a *prima facie* case of obviousness.

First, the combination does not teach all the limitations of at least claims 19, 22, and 30. Regarding claim 19, Kris is alleged to “teach a polypeptide substrate (par. 18-19), wherein the one polypeptide comprises a first label and substrate for kinase (labeled antibodies bind to substrate, and therefore a single polypeptide comprises the substrate and first label, par. 256-258).” Applicants note, however, that the substrate and the antibody are in fact two separate molecules. The fact that the labeled antibody can bind the phosphorylated substrate does not mean that the antibody and substrate are included on a single polypeptide. Whether they are bound to each other or not, they are still two distinct polypeptides and thus fail to meet the limitations of claim 19, which specifies that one polypeptide comprises the first label and the substrate.

Also with respect to claim 19, the Action alleges that Kris teaches the first label located at the tyrosine residue. However, Applicants note that the label of Kris is located on the antibody; the label not found on the substrate at all, much less at the tyrosine residue of the substrate. Furthermore, although the Action alleges that the label “exhibits a first signal when the residue is not phosphorylated and the second signal when the” residue is phosphorylated, Applicants note that the signal from the label is not actually responsive to the state of the substrate.

With respect to claims 22 and 30, the combination of Ting, Burbaum, Walker, and Kris fails to teach at least location of the one or more caging groups on a residue phosphorylated by the kinase. Further, with respect to claim 22 which depends from claim 21, as described above, Ting (and thus the combination of Ting, Burbaum, Walker, and Kris) fails to teach a sensor such as that of claim 22 in which the labels interact when the substrate is not phosphorylated and do not interact when the substrate is phosphorylated.

The combination of Ting, Burbaum, Walker, and Kris thus does not teach all the limitations of the indicated claims. Moreover, with respect to all the claims, motivation to combine the teachings of the references is lacking. As described in some detail above and as discussed with the Examiner, motivation for combining the teachings of Ting, Burbaum, and Walker is clearly lacking; motivation for adding the teachings of Kris is similarly lacking. In addition, there is no reasonable expectation of success. Applicants respectfully request the rejections be withdrawn.

Item 8

Claims 47-56 and 59-60 were rejected for alleged obviousness under 35 USC 103(a) over Ting et al. in view of Burbaum et al. further in view of Walker et al. and Fischer et al. Claims 59 and 60 have been cancelled as noted above, rendering the rejection moot with respect to these claims. To the extent the rejections are applied to the amended claims, Applicants respectfully traverse.

The combination of Ting, Burbaum, Walker, and Fischer does not meet the requirements for a *prima facie* case of obviousness.

With respect to claims 50 and 55, the combination does not teach all the limitations of the claims. For example, the combination fails to teach at least covalent attachment of a cellular or subcellular delivery module that is reversible by light.

In addition, with respect to all the claims, motivation to combine the teachings of the references is lacking. As described in some detail above and as discussed with the Examiner, motivation for combining the teachings of Ting, Burbaum, and Walker is lacking; motivation for combining the teachings of all four references is similarly lacking. In addition, there is no reasonable expectation of success. Applicants respectfully request the rejections be withdrawn.

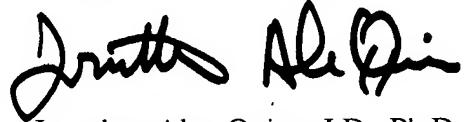
### CONCLUSION

In view of the foregoing, Applicant(s) believe(s) all claims now pending in this application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the claims are deemed not to be in condition for allowance after consideration of this Response, **a telephone interview with the Examiner is hereby requested**. Please telephone the undersigned at (510) 337-7871 to schedule an interview.

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Attachments:

- 1) A petition to extend the period of response for one month;
- 2) A transmittal sheet;
- 3) A fee transmittal sheet; and
- 4) A receipt indication postcard.